Rare disease

Acute encephalopathy with bilateral thalamotegmental involvement and a benign course: a case report from Brazil

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Summary

This rare encephalopathy that generally affects children is preceded by a respiratory infection and fever associated with convulsions and may progress to coma. Outcome is catastrophic in most cases. This case report describes a Brazilian child of African descent with fever, cephalgia and bilateral amaurosis, who evolved to coma with pyramidal signs and associated convulsions. MRI showed diffuse, symmetrical lesions in the thalamotegmental region and brainstem. Following administration of methylprednisolone, the clinical condition of the patient improved and the brain lesions regressed, leaving the child with no current neurological deficits. This was a case of acute postinfectious encephalopathy, involving various brain structures. Outcome was favourable with no sequelae following therapy. This case was atypical due to the bilateral visual involvement and extensive encephalic lesions in a child of African descent with no neurological sequelae following therapy. No other similar cases have been reported in the literature.

BACKGROUND

Acute encephalopathy associated with bilateral thalamotegmental lesions is a condition whose aetiology is yet to be fully clarified. It generally affects children and adolescents of both sexes. It is preceded by several days of fever and symptoms suggestive of upper respiratory tract involvement. The condition generally progresses rapidly to stupor and coma associated with generalised convulsions and decorticate and decerebrate rigidity, albeit with no associated focal neurological or meningeal signs.¹ Death generally occurs in the first few days following the onset of symptoms. It is believed that fewer than 10% of the individuals affected by this syndrome recover from the disease without any neurological damage.^{1 2}

The prevalence of this encephalopathy is higher in countries of eastern Asia, although some isolated cases have been reported in other parts of the world. The clinical presentation of the individuals with this syndrome consists of rapid neurological deterioration with an increase in protein levels detected in cerebrospinal fluid analysis and the presence of characteristic brain lesions. Diagnosis is based on neuroimaging findings and on postmortem neuropathological evaluation.²

Clinical course of the disease is variable; however, in the cases analysed to date the mortality is high. Although some patients recover from the deficits naturally, in the majority of cases there are irreversible neurological sequelae. Therapeutic management is limited to support therapy although some individuals have benefited from the use of corticosteroids or immunoglobulins in the early stages of the disease.^{3 4}

The aim of this paper is to describe the clinical and radiological characteristics of this rare encephalopathy in the first case of its kind to be described in a Brazilian child of African descent who recovered rapidly following pulse therapy. In the present case, the syndrome was associated

with bilateral loss of vision, an aspect that has not been described in any other similar cases.

CASE PRESENTATION

A 9-year-old Brazilian girl of African descent presented with no associated history of morbidity. An episode of fever and cephalgia evolved to unilateral, then bilateral loss of vision associated with adynamia and loss of strength in all four limbs. Neurological examination revealed bilateral amaurosis with a reduction in photomotor reflex and Babinski sign in the left foot.

There was a decrease in the level of consciousness in the following hours, in conjunction with bilateral paralytic mydriasis associated with chewing movements that were interpreted as convulsions, leading to initiation of anti-convulsant therapy. At this time, examination revealed a decrease in the patient's level of consciousness, her pupils were isochoric and eye movements were slow, tetraparesis was present with increased deep tendon reflexes, bilateral Babinski sign but no sign of meningeal irritation. Over the following days, the patient went into a coma vigil with bilateral mydriasis, tetraparesis and bilateral positive Babinski and Hoffman signs. At this time, a regimen of pulse therapy was initiated that resulted in an improvement in the child's level of consciousness and responsiveness to verbal requests; however, both pupils remained mydriatic, photomotor reflex was slow and tetraparesis, predominantly crural, persisted on the left side. A second cycle of pulse therapy was initiated 2 weeks after the first and the general state of the patient improved.

Three days after treatment, she had an episode of syncope and significant behavioural change, becoming aggressive and with mood swings. She had what appeared to be an atonic absence seizure of short duration associated with chewing movements and clonus of the lower limbs. A further series of pulse therapy was administered.

Figure 1 Brain MRI performed 8 days after the onset of symptoms, prior to the first cycle of pulse therapy. Axial (A) and coronal (B) planes in T2, fluid-attenuated inversion recovery (FLAIR) (C–F), showing lesions with a predominant hypersignal in the thalamic region and bilaterally in the posterior limb of the internal capsule and temporal lobe, claustrum, hippocampus, amygdalae, hypothalamus, external capsule, mesencephalus, pons and middle cerebellar peduncles. The coronal plane in T2 (B) shows a large part of the affected areas, highlighting the extension of the lesions from the thalamic region to the pons.

INVESTIGATIONS

Lumbar puncture was performed at the onset of symptoms, revealing slight pleocytosis. EEG showed diffuse, bilateral waves of 2–5 Hz. MRI carried out on the 8th day of the disease revealed the presence of symmetrical, bilateral lesions in the thalamotegmental region, extending as far as the brainstem (figure 1). After the initial cycle of pulse therapy, a second MRI (carried out on the 30th day of the clinical evolution) was performed, showing almost total regression of the pre-existing lesions (figure 2).

DIFFERENTIAL DIAGNOSIS

1. Acute disseminated encephalomyelitis
2. Reye's syndrome
3. Acute toxic encephalopathy.

TREATMENT

1. Clinical support measures
2. Anticonvulsants (clonazepam and phenytoin)
3. Methylprednisolone (500 mg/day) for three treatment cycles.

OUTCOME AND FOLLOW-UP

In the days following treatment, a progressive improvement was seen in the patient's level of consciousness, motor deficit and behaviour. She was discharged from hospital around 45 days after the onset of symptoms, still in use of clonazepam and phenytoin. Currently, 2 years

after the onset of symptoms, the patient has no neurological deficits and is not in use of any medication.

DISCUSSION

Acute encephalopathy with thalamotegmental involvement in children is an extremely rare form of acute encephalopathy.⁵ It is a condition more often reported in countries of eastern Asia such as Japan, Taiwan and South Korea; nevertheless, some cases have been described in Europe and in the Americas.^{3 6–9}

In 1995, Mizuguchi⁴ described this new condition as 'acute necrotising encephalopathy of childhood'. The reason for its prevalence in this particular age group is unknown; however, it is most probably an underdiagnosed condition and is certainly more common than is presumed.^{4 10–12} Its pathophysiology is unknown, although it is believed to involve an immune-mediated reaction following a prior viral infection. The virus most frequently associated with the syndrome is influenza A (predominantly in Japan and Taiwan), although other viruses such as influenza B, varicella, herpes simplex, rubella, herpes virus types 6 and 7 and adenovirus, in addition to *Mycoplasma pneumoniae* have also been related to this condition.^{9 13}

At onset this encephalopathy generally manifests itself in the form of convulsions, progressive neurological deficits that gradually diminish the patient's level of consciousness until he/she becomes comatose. In the present case, the onset of the disease was unusual, since it involved a

Figure 2 Brain MRI performed 20 days after the first examination and after the first cycle of pulse therapy. FLAIR images showing almost total regression of the lesions that had been affecting the thalami, internal capsule, external capsule and claustrum, brainstem, middle cerebellar peduncle, hippocampus and amygdalae. Note that only a few minimal lesions and foci of haemorrhagic transformations remain in the brainstem, principally in the pontine region, arrows (B, C).

progressive loss of vision (initially unilateral amaurosis that soon became bilateral, associated with a reduction in photomotor reflex and bilateral paralytic mydriasis), signs of bilateral involvement of the corticospinal tract and a marked change in behaviour and decrease in the level of consciousness. Supplementary tests confirmed the syndrome – diffuse bilateral encephalic involvement as shown by MRI, a slight increase in proteins in cerebrospinal fluid and diffuse bilateral abnormalities as detected by EEG. Treatment consisted of prednisolone immediately following the onset of symptoms, which is one of the measures recommended in these cases although it is not always effective in resolving symptoms, principally if initiated during the chronic phase of the disease.

Consequently this was a complex case with pleomorphic clinical and semiotic presentation. The remarkable feature in the course of this case was the presence of bilateral

visual involvement signalling the onset of the syndrome, a fact that has not yet been reported in any of the cases previously described. According to Okumura *et al*,^{14–16} areas of hypoperfusion were found in various regions, including the occipital lobe, a fact that may explain the sudden onset of visual impairment, since in this syndrome no inflammatory or demyelinating lesion has been recorded that would provide an anatomopathological basis justifying a lesion on the visual pathway. The cases studied up to the present time have shown the classic abnormalities found with this condition, including necrosis, cerebral oedema, petechiae and congestion of the thalamus, white substance and brainstem.

Evaluation of cerebrospinal fluid reveals moderate pleocytosis associated with a slight increase in protein levels.^{4–5} EEG presentation is more evident during the acute phase of the disease, with alterations to basic

rhythm, generally in the form of generalised, slow non-synchronous waves.¹⁴

On the other hand, during the subacute phase when abnormalities in consciousness are present, neuroradiological evaluation may indicate lesions that are generally found in the cortical region and white substance in the form of multifocal involvement, affecting the thalamus, internal capsule, hypothalamus, brainstem and even the cerebellum, which in the majority of cases is indicative of poor prognosis. The change in magnetic resonance signal intensity at thalamic level generally reflects the time of evolution of haematomas and the progression of these thalamic lesions is generally accompanied by a decrease in the level of consciousness, probably due to the bilateral involvement of thalamic fibres, which are projected over the cortex. In spectroscopic analyses by magnetic resonance, the abnormal presence of lactate has been found in the thalamic region. On the other hand, in case studies using single photon emission tomography in the subacute and chronic phases, abnormalities in bilateral perfusion have been found, particularly in regions such as the frontal, temporal and occipital lobes.^{2 14 17–19}

A necropsic study of patients with these abnormalities showed macroscopic colour changes in the thalamic region suggestive of haemorrhagia and necrosis. Areas of venous and capillary congestion were seen, associated with petechiae. No signs of inflammatory infiltrates or reactive proliferation of the astrocytes or the microglia cells were found.^{5 20}

Therapy is limited and not always promising. In addition to clinical support measures, methylprednisolone, dexamethasone and intravenous immunoglobulins may be used, as well as mannitol therapy. Okumura *et al*^{14–16} failed to find any difference between the use of methylprednisolone and dexamethasone in the treatment of these patients; nevertheless, it has been suggested that the site of the lesion may affect therapeutic response. According to a study carried out in 34 patients with this syndrome who used corticosteroids, the majority of individuals with no brainstem lesions responded satisfactorily to treatment, unlike those with lesions in the brainstem, who responded poorly to medication and progressed with significant persistent sequelae.¹⁵ In cases associated with convulsions, the use of phenytoin, phenobarbital, valproic acid and clonazepam is recommended, and clinical response is generally good.¹⁴

The majority of Japanese patients with this encephalopathy were reported to have severe sequelae with a strong negative effect on their quality of life. A small percentage of the patients studied had complete remission from symptoms. Imaging studies carried out on these children, spontaneous concomitant regression of brain lesions was seen during the course of the disease. Conversely, the deaths that occurred happened during the acute phase of the development of symptoms.^{1 4 16 21}

The greatest similarity between the present case report and the previous studies involving this acute encephalopathy resides in the progressive neurological deterioration in a child following an acute viral episode associated with convulsions and diffuse behavioural abnormalities, culminating in coma. Nevertheless, the bilateral visual involvement and the exuberant clinical recovery following therapy with methylprednisolone render this case even more unusual and noteworthy.

Learning points

- Acute encephalopathy with thalamotegmental involvement is a rare condition with a poor prognosis in the majority of cases.
- It is a common disease in eastern Asian populations and generally affects school-aged children. It is associated with convulsions and changes in the level of consciousness, generally after an episode of fever with no other complications.
- There is no specific therapy for this disease. At present, the therapy consists of general supportive and conservative treatments and administration of corticosteroid at the acute stage.
- This case illustrates a rare presentation of this disease (with bilateral visual involvement) in a child of African descent, who evolved satisfactorily following therapy with methylprednisolone.

Competing interests None.

Patient consent Obtained.

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